Cyclooxygenase-2 expression and its association with thyroid lesions

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Abstract

Cyclooxygenase (COX), also known as prostaglandin H synthase, catalyses the formation of prostaglandins from arachidonic acid. It can be expressed in response to various stimuli, such as hormones, mitogens, cytokines, other inflammatory mediators and growth factors. The product of COX-2 activity has been implicated in carcinogenesis by promoting angiogenesis, inhibiting apoptosis, increasing cell invasion and stimulating cell proliferation. It has also been proved that the regular intake of non-steroidal anti-inflammatory drugs (NSAIDs) decreases the risk of developing colon and breast cancers. Thus, it speaks for an important role of COX-2 in growth processes of various types of neoplasms. The connection between COX-2 activity and carcinogenesis has also been examined in human thyroid neoplasms. COX-2 overexpression has been reported in thyroid cancers and also in inflammatory conditions. In consequence there is significant interest whether COX-2 could be of importance as a molecular marker of malignancy in the case of thyroid carcinoma.

Key words: cyclooxygenase-2 gene, expression, thyroid lesions.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase (COX), which is the key enzyme in biosynthesis of proinflammatory prostaglandins from arachidonic acid [1]. This notion has been supported by suppression of inflammatory responses in a number of clinical courses with experimental animals, followed by analysis of human cell cultures. It has been proved that regular intake of NSAIDs decreases the risk of developing colon cancer [2, 3]. Non-steroidal anti-inflammatory drugs have also been of interest for researchers, as to whether their regular intake could possibly decrease the risk of developing other types of cancer.

Cyclooxygenase enzymes

The cyclooxygenases are a group of enzymes that catalyse the formation of prostaglandins from arachidonic acid. The *COX-1* gene is located on chromosome 9q and encodes a 66-kDa protein, whereas the *COX-2* gene is found on chromosome 1 and encodes a 70-kDa protein, which has 61% homology with the product of COX-1 [4].

Cyclooxygenase-1 is a constitutive form, thought to be a housekeeping gene, with constant levels of expression in most tissues. It is indispensable in order to maintain physiological functions, such as gastric cytoprotection, vascular homeostasis and kidney function (mediated by prostaglandins); also it regulates normal platelet function, which is mediated by thromboxane [5]. As regards the thyroid gland, COX-1 has not been a subject of excessive interest, perhaps except for medullary thyroid carcinoma [6, 7]. On the other hand, COX-2 is expressed at baseline levels and is frequently undetectable in normal tissues. The relation of COX-2 to pathological phenomena in the thyroid gland seems to be much closer and is a subject of intensive research. Additionally, it should be mentioned that lipoxygenase (LOX), like COX-1, has not aroused more interest as regards the thyroid.

Besides NSAIDs, also corticosteroids decrease COX-2 expression or downregulate transcript isoforms of COX-2 [8, 9]. It has recently been reported that aurothiomalate inhibits COX-2 expression in chondrocytes and in human cartilage, possibly through its effects on COX-2 mRNA stability [10]. Also, studies on certain plant extracts' effect on COX-2 expression in cancer cells are being conducted, but the subject requires further elucidation [11].

Cyclooxygenase-2 and carcinogenesis

It can be expressed in response to various stimuli, such as hormones, mitogens, cytokines, other inflammatory mediators and growth factors via protein kinase C and *Ras*-mediated signalling [12, 13]. The product of COX-2 activity has been implicated in carcinogenesis by promoting angiogenesis, inhibiting apoptosis, increasing cell invasion and stimulating cell proliferation [14-17]. It also modulates vascular endothelial growth factor (VEGF) synthesis; this action promotes angiogenesis and decreases immunity towards cancer cells [18, 19].

Recent studies have shown that up-regulation of COX-2 is associated with numerous neoplasms, including head and neck squamous cell, colorectal, breast, lung, skin, stomach, liver, pancreas, bladder, ovary and prostate cancers [20-35]. Epidemiological data suggest that the regular use of NSAIDs can significantly lower the risk of developing breast cancer, by approximately 50%. A prospective study of over 600,000 adults has indicated that aspirin use decreases the risk of colon cancer by up to 50%. A prospective cohort of 49,700 male health professionals has shown that a regular intake of aspirin lowers the risk of metastatic and fatal colon cancers, whereas "The Nurses' Health Study" has found a decreased risk of colorectal cancer among women taking two or more aspirin tablets per week, for 10 or more consecutive years [36, 37].

No epidemiological and/or randomized studies have – so far – been performed in humans to determine the protective properties of selective COX-2 inhibitors, but experimental animal data are fairly promising. COX-2 knockout mice develop about 75% fewer chemically induced skin papilloma [38]. In another study, null mutation for COX-2 in ApcΔ716 mice (a murine model of familial adenomatosis) caused a marked reduction of intestinal polyps and suppressed angiogenesis because of lowered expression of VEGF. Administration of COX-2 inhibitor caused further polyp reduction in that case [39, 40].

Some of the published studies suggest an important relationship between COX-2 activity and the severity of illness, especially in carcinomas of the gastrointestinal tract. It concerns mostly the depth of invasion, the size of the tumour and the amount of metastases into lymph nodes. In these cases, the main source of increased COX-2 protein product is not fibroblasts or proinflammatory cells but tumour cells themselves [13].

Cyclooxygenase-2 and thyroid cancer

Thyroid cancer is the most common endocrine malignancy and its most frequent types include well-differentiated thyroid cancers – papillary (PTC) and follicular (FTC) types, accounting for approximately 95% of all thyroid cancers.

The connection between COX-2 activity and carcinogenesis has also been examined in human thyroid neoplasms. The involvement of the COX pathway in the process of inflammation and in cellular growth in the thyroid has been considered. Interestingly, in the study of Larson *et al.* [41], patients with Hashimoto thyroiditis were three times more likely to have thyroid cancer, suggesting a strong link between chronic inflammation and cancer development.

There are also many well-known genetic alterations associated with thyroid cancer that could account for an increase in COX-2 expression. *Ras* oncogene mutations have been found with high frequency in benign and malignant thyroid tumours, in all stages of human thyroid tumourigenesis [42, 43]. Fibroblasts, transformed with a mutant *Ha-Ras* oncogene respond with a rapid induction of COX-2 [44]. Also, *Ha-Ras* expression in intestinal epithelial cells leads to expression of COX-2 [45].

Another genetic factor is the *RET* proto-oncogene. It has previously been shown to activate *Ras*, and thus it could indirectly lead to COX-2 activation. Whether *RET* could activate COX-2 in any other way is a matter of further investigation [46].

All but one of the conducted studies demonstrate overexpression of COX-2 in cases of PTC and FTC. In the immunohistochemical study of Ito *et al.* [47], there were 9 COX-2-negative cases out of 49 PTC

(18.4%). The authors also suggested a significant reduction of COX-2 levels in elderly patients (above 54 years old), in patients with large tumours and with advanced disease stages, as well as with the presence of solid, scirrhous or trabecular growth pattern.

However, in the study of Kajita *et al.* [48] and Garcia-Gonzales *et al.* [49] age was associated with an increased incidence of PTC. The results of Kajita *et al.* [48] did not show any significant differences in COX-2 expression between normal thyroid tissue and PTC, because of the observed variation in mRNA levels. The authors also performed an *in vitro* study with the TPC-1 thyroid carcinoma cell line and NS-398, a COX-2 enzymatic activity specific inhibitor, showing suppression of tumour cell growth. They confirmed the role of COX-2 in the growth of papillary thyroid cell lines [48].

Cornetta *et al.* [50] examined a variety of thyroid tissue specimens. COX-2 staining was not observed in specimens obtained from normal thyroid tissue, multinodular goitre, or anaplastic carcinoma. An analysis of Hashimoto's thyroiditis revealed COX-2 expression in follicular epithelium and lymphocytic infiltrates, as well as in cells of FTC and PTC [50].

The immunohistochemical study of Lee *et al.* [51] showed prominent expression of COX-2 in thyroiditis, and in benign and malignant thyroid lesions, but not in normal thyroid tissue. Nor did the authors observe any difference in the levels of COX-2 expression between different tumour tissue types. Because of the same intensity of COX-2 staining found in thyroiditis, and benign and malignant thyroid lesions, the authors concluded that COX-2 expression is unlikely to be related to the progression of thyroid disease.

Specht *et al.* [52] reported overexpression of COX-2 in 8 out of 10 cases of thyroid cancer, specific for tumour cells but not for surrounding stroma. They found that both COX-2 mRNA and protein increase in malignant thyroid nodules, when compared to benign nodules and adjacent normal thyroid tissue.

The results of experiments with ApcΔ716 knockout mice suggest that the induction of COX-2 is a very early event in colon carcinogenesis. That thesis has been supported by Garcia-Gonzales *et al.* [49], who suggest that even though COX-2 plays an important role in the progression of all thyroid cancers, in the case of PTC it seems to be more important only in the early stages of the cancer.

Rather limited data can be traced on the role of COX-2 in follicular neoplasms, due to the small number of patients enrolled into clinical studies. FTC is believed to arise from pre-existing follicular thyroid adenoma (FTA), indicating that FTA is a prominent candidate for a precursor of FTC, although this statement is still to be confirmed. In the largest published series of cases evaluating follicular neoplasms with COX-2, Nose *et al.* [53] assessed immunoreactivity in 41 FTC and 23 FTA; they observed strong COX-2 expression in all the cases. In the earlier cited paper by Ito *et al.* [47], the authors performed immunohistochemical staining of COX-2 in 22 FTC and 15 FTA. Cyclooxygenase-2 overexpression was found in 40.9% of FTC and 20% of FTA but without any statistical significance in COX-2 expression between those two clinical entities. Cyclooxygenase-2 overexpression was also found in the study of Haynik *et al.* [54]; that study included 34 patients with FTC and demonstrated increased COX-2 expression in 26% of them. There was no association between positive staining for COX-2 and other prognostic indicators (vascular invasion, capsular penetration, necrosis or Hürthle cell lesion) but the authors found a higher percentage of recurrences or metastases and of tumours that caused death in cases with COX-2-positive staining [54].

On the other hand, the experimental study by Fuhrer *et al.* [55], using real time PCR, showed similar COX-2 mRNA expression levels in benign and malignant follicular neoplasms, normal thyroid tissue and Graves' disease samples. The authors concluded that COX-2 usefulness as a molecular marker for follicular thyroid neoplasia is markedly limited.

Cyclooxygenase-2 and thyroiditis

Cyclooxygenase-2 overexpression has been reported not only in thyroid cancers but also in inflammatory conditions, such as thyroiditis. Chronic inflammation, leading to neoplastic transformation by promoting genomic instability, is a well established clinical phenomenon. The relation of thyroid neoplasm to Hashimoto disease has already been reported in a very early paper [56].

An association between Hashimoto thyroiditis and thyroid cancer remains controversial, with various authors reporting different frequencies, e.g., as high as 43.8% [41] or 11-36% [57]. Another study shows that transformed thyrocytes were able to induce COX-2 expression in follicular cells and to secrete IL-6 in response to IL-1β and TNF-α [58]. Therefore, COX-2 expression in Hashimoto's thyroiditis may predispose the thyroid follicular epithelium to secrete proinflammatory cytokines, such as IL-6, potentiating an inflammatory response and the risk of developing thyroid carcinoma [50].

Enhanced expression of COX-2 in lymphocytic thyroiditis (Hashimoto's thyroiditis) suggests an important role of this enzyme in the inflammatory processes of the thyroid gland. There have been several studies supporting this thesis, based on immunohistochemical analysis, showing

overexpression of COX-2 in inflammatory thyroid tissue [49-53]. However, in a recent study, Lo *et al.* [59], using immunohistochemical evaluation of examined specimens, did not detect COX-2 expression in lymphocytic thyroiditis.

In conclusions, the usefulness of COX-2 as a marker of thyroid malignancy has been challenged, but its potential role in carcinogenesis has aroused significant interest.

Fine needle aspiration biopsy has become a critical component in the management of thyroid nodules. It allows the number of cases requiring surgical treatment to be decreased from 67% to 44%. Also the percentage of surgically treated carcinomas in those nodules increased from 14% up to 29% [60]. Preoperative discrimination of thyroid malignancy, using not only cytopathology but also a molecular marker, would enhance proper diagnosis.

The frequent negativity of COX-2 staining in undifferentiated thyroid carcinomas and FTC indicates that COX-2 is not always useful as a marker of malignancy. When discussing this matter, we should consider the important finding that COX-2 expression was found to be significantly higher in PTC. Therefore, its application in diagnosing thyroid malignancy would be limited to PTC cases. Accordingly, COX-2 expression has been documented in a relatively large number of patients with PTC. Therefore, it could be useful in patients with diagnostic difficulties and suspicion of PTC.

Due to promising preclinical data, there are some clinical studies assessing the efficacy of selective COX-2 inhibitors in various malignancies, either alone or in combination with other treatment possibilities. Based on the above-mentioned studies, it would be important to establish whether selective COX-2 inhibitors could play some role in prevention of thyroid malignancies.

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